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Four-year changes in central fatness, risk of diabetes, and metabolic control in older adults: a cohort study with mediation analysis

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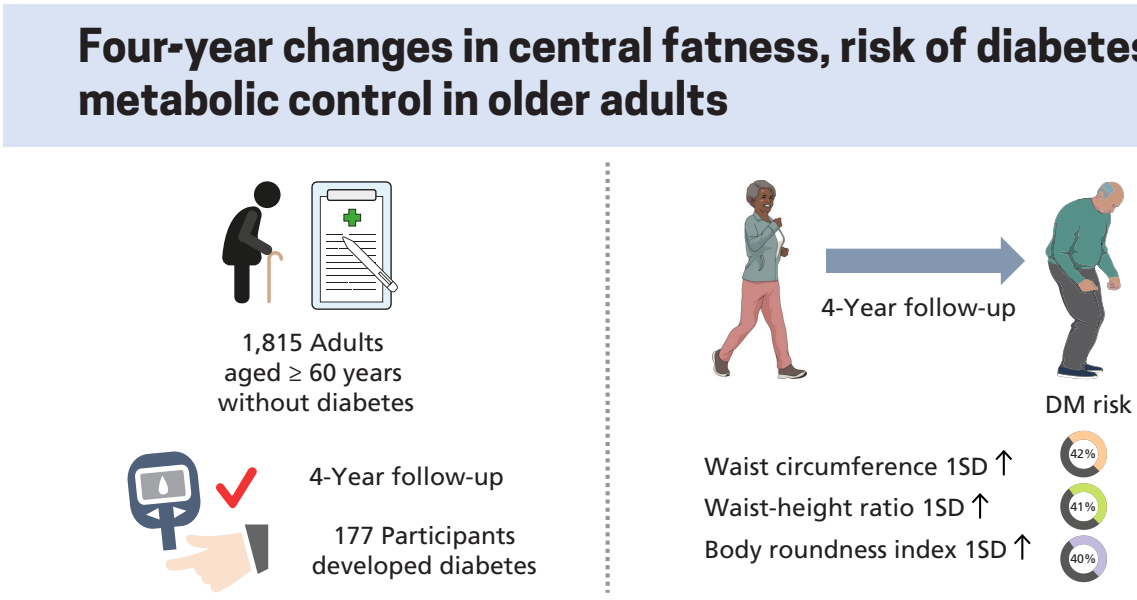

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Background/Aims: Older adults are vulnerable to central obesity, while the association of changes in central fatness with risk of diabetes and metabolic control has not been investigated among this particular population. This study was aimed to address these issues.

Methods: A total of 1,815 adults aged ≥ 60 years without diabetes at baseline were followed for 4 years. Incident diabetes was ascertained based on plasma glucose, hemoglobin A1c, medical history, and/or the use of anti-diabetic drugs. Central fatness was assessed by waist circumference (WC), waist-height ratio (WHtR), and body roundness index (BRI). Logistic regression analyses were used to assess the association of changes in central fatness with risk of diabetes, along with dose-response and mediation analyses.

Results: During the 4-year follow-up, 177 participants developed diabetes. The risk of diabetes was increased by 42%, 41%, and 40% per 1 standard deviation increases in WC, WHtR, and BRI, respectively, in multivariable-adjusted models (all $p < 0.01$). Moreover, these relationships were all linearly-shaped (all $p_{nonlinearity} \geq 0.11$). Increases in WC, WHtR, and BRI correlated with increases in hemoglobin A1c, triglycerides-and-glucose index, triglycerides, white blood cell, and C-reactive protein (all $p \leq 0.04$). Yet only changes in hemoglobin A1c and triglycerides-and-glucose index were identified as the possible mediators for risk of diabetes, with their mediating effect being about 35% and 21%, respectively.

Conclusions: Increases in central fatness were related to elevated risk of diabetes, and this association might be partly explained by the worsening of glycemic control and insulin resistance in older adults.

Keywords: Aged; Obesity; Follow-up studies; Insulin resistance; Mediation analysis

INTRODUCTION

Diabetes has become a worldwide public health challenge [1], in particular for the aging population [2]. The latest national survey conducted in China has suggested that nearly 30% of the older adults aged ≥ 60 years have diabetes [2]. Moreover, older adults with diabetes have a higher risk for geriatric syndromes such as depression [3], and exhibit an increased risk for cardiovascular and all-cause mortality [4,5], compared with those without diabetes. These results, collectively, indicate that the presence of diabetes may complicate the management of aging, and thus, highlight the importance of identifying risk factors that could be modified to prevent diabetes in older adults.

Central obesity is a well-recognized risk factor for diabetes [6]. However, there is scarce evidence with regard to changes in central fatness with risk of diabetes in older adults, who are vulnerable to such changes, because of the lowered lipid removal rate or accelerated lipid uptake rate in adipose tissue [7] and the reductions in the amounts of physical activity during ageing [8]. Moreover, in recent years there is evidence that indicators of central fatness, such as body roundness index (BRI), may carry superior predictive abilities for diabetes to general fatness indicator—body mass index (BMI) [9,10]. Yet it is unclear whether such a difference exists with regard to their changes in older adults. Furthermore, a previous meta-analysis suggested that intervention-based body fat reduction improves metabolic control such as blood pressure, glycemic control, and lipid profiles [11]. However, no studies have examined whether changes in central fatness correlated with changes in these cardiometabolic factors, and the change of which factor may mediate the association of changes in central fatness with risk of diabetes in older adults.

Therefore, this study aimed to evaluate the association of changes in central fatness (assessed by waist circumference [WC], waist-height ratio [WHtR], and BRI) with risk of diabetes in older adults who were followed for 4 years. We also used dose-response analysis to depict their relationships, subgroup analysis to explore the moderators, and mediation analysis to identify the mediators. Furthermore, we made comparisons on the predictive abilities of changes in central fatness with changes in general fatness to address the concerns raised in previous studies [6,12].

METHODS

Study population

The China Health and Retirement Longitudinal Study

(CHARLS) is an ongoing cohort study that enrolled a nationally representative sample of community-dwellers aged ≥ 45 years in China [13,14]. The baseline survey was conducted in 2011 to 2012 and included 17,708 participants. The study design of CHARLS was approved by the ethical review committee at Peking University (approval No. IRB 00001052-11014), and informed consent was obtained from each participant. The details about the sampling and design of CHARLS have been provided elsewhere [13].

In this study participants who were aged ≥ 60 years at baseline and followed for 4 years were eligible for inclusion. Of them, 2,909 had blood samples collected at baseline and in 2015. After excluding participants with incomplete information on body weight, WC, blood pressure, blood-based biomarkers such as plasma glucose, hemoglobin A1c (HbA1c), total cholesterol (TC), or C-reactive protein (CRP) at baseline or in 2015 (n = 338), being diagnosed with diabetes before the survey in 2015 (n = 513), having data considered abnormal or as outliers on body weight, height, BMI, WC, blood pressure, or their changes (n = 243), 1,815 participants were finally included (Supplementary Fig. 1).

Demographic, anthropometric, and biochemical variables

Demographic data including age, sex, education, smoking, drinking, and disease history (e.g., hypertension, cardiovascular disease, kidney disease) were collected using a pre-designed questionnaire, and anthropometric variables, such as body weight, height, and WC, were measured using standard protocols described in the CHARLS handbook [13]. Blood pressure was measured three times, at a 45-second interval, using Omron™ HEM-7200 Monitor (Omron Co. LTD., Dalian, China), and its average value was used in the present study.

BMI, WHtR, and BRI were calculated using the following equations [6,9].

$$\text{BMI} = \frac{\text{body weight (kg)}}{\text{height (m)}^2}$$

$$\text{WHtR} = \frac{\text{WC (m)}}{\text{height (m)}}$$

$$\text{BRI} = 364.2 - 365.5 \times \sqrt{1 - \frac{(\text{WC (m)}/(2\pi))^2}{(0.5 \times \text{height (m)})^2}}$$

Blood samples were collected in the morning, with their plasma being centrifuged for measurements of HbA1c, glucose, TC, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), as well as CRP [14]. Blood count analysis for white blood cells (WBCs) was conducted at the local county health centers. The triglycerides-and-glucose (TyG) index, which is recognized as a marker for insulin resistance [15], was calculated as:

Assessment of walking speed

Participants in this study were guided to walk twice on a straight 2.5-m flat course, with walking time being recorded by a stopwatch to calculate walking speed [13]. This was used to reflect the physical wellbeing/performance and the level of physical activity of an individual [16,17].

Definitions

In this study incident diabetes is defined as: fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL), random plasma glucose ≥ 11.1 mmol/L (200 mg/dL), HbA1c ≥ 6.5% (48 mmol/mol), medical history, and/or the use of anti-diabetic drugs [18]. BMI ≥ 24 kg/m^2 is classified as overweight/obesity, and < 24 kg/m^2 as normal weight. Hypertension is ascertained by: systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, medial history, and/or the use of antihypertensive drugs. Dyslipidemia is defined as: TC ≥ 240 mg/dL, LDL-C ≥ 160 mg/dL, HDL-C < 40 mg/dL, TG ≥ 200 mg/dL, medial history, and/or the use of lipid-lowing agents [19].

Changes in central fatness were defined as the change scores in WC, WHtR, or BRI from baseline. Similarly, changes in glycemic control, lipid profiles and inflammatory markers were calculated using the same methods.

Statistical analysis

Data were expressed as means ± standard deviations (SDs) for continuous variables and numbers (%) for categorical variables, unless otherwise stated. Unpaired *t* test and chi-square test were used to compare the difference between groups. Changes in central fatness were evaluated in the following two ways: (1) as continuous variables expressed as per 1 SD change; and (2) as categorical variables, which were divided into tertiles: loss (the lowest tertile of the change), stable (the middle tertile), and gain (the highest tertile). Logistic regression analyses were conducted to ob-

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tain the odds ratios (ORs) and 95% confidence intervals (CIs) for risk of diabetes in relation to changes in central fatness using an unadjusted model, and then the multivariable models that include age, sex, and BMI (Model 1), as well as history of smoking and drinking, disease status (hypertension, dyslipidemia, and cardiovascular disease), SBP, HbA1c, TC/HDL-C, UA, CRP, and walking speed at baseline (Model 2). To further assess the relationship of changes in central fatness with risk of diabetes, dose-response analyses, which were modeled with the restricted cubic splines, were introduced [20]. Moreover, subgroup analyses on the basis of sex (male vs. female), age category (60–70 years vs. ≥ 70 years), overweight/obesity (yes vs. no), history of smoking and drinking (yes vs. no), walking speed (fast vs. slow) were also performed. The predictive abilities for diabetes with regard to changes in central fatness were assessed by the area under the receiver operating characteristic curves (AUROC), and compared according to the method described previously [21,22]. Multivariable linear regression analysis adjusting for age, sex, and BMI was employed to investigate the relationship of changes in central fatness with changes in several cardiometabolic markers including blood pressure, glycemic control, lipid profiles, and inflammatory markers. We also utilized mediation analysis to explore the mediating role of the changes in these cardiometabolic markers for risk of diabetes. All analyses were conducted using Stata software version 14.0 (StataCorp., College Station, TX, USA), with $p < 0.05$ considered statistically significant.

RESULTS

Characteristics of enrolled participants

During the 4-year follow-up, 177 of the 1,815 participants developed diabetes, and their baseline characteristics are shown in Table 1 and Supplementary Table 1. Compared with participants who did not develop diabetes, those who did were more likely to present with hypertension, had larger BMI, WC, WHtR, and BRI, and bigger values of FPG, HbA1c, TyG index, TC, TG, and UA, and exhibited a higher degree of inflammation assessed by WBC and CRP. Yet the percentages of smokers and drinkers as well as the walking speed did not differ between groups (all $p \geq 0.63$).

Of the enrolled participants, their body weight was minorly changed in the follow-up years from baseline ($p = 0.20$), but their BMI, WC, WHtR, and BRI were increased on average (all $p < 0.01$). For participants developed diabetes, they had larger increases in WC, WHtR, and BRI than those remained free of diabetes (all $p < 0.01$). Further analysis showed that the risk of diabetes was increased by 44%, 40%, and 37% per 1 SD higher of WC, WHtR, and BRI at baseline, respectively, in multivariable-adjusted model (all $p < 0.05$) (Supplementary Table 2); and their relationship was found to be all linearly-shaped (all $p_{nonlinearity} \geq 0.38$) (Supplementary Fig. 2).

Changes in central fatness and risk of diabetes

The ORs for diabetes associated with changes in central fatness are presented in Table 2, and the baseline characteristics of the participants among the tertiles of these changes are summarized in Supplementary Table 3. In unadjusted model, the ORs for diabetes were 1.31 (95% CI, 1.12 to 1.54), 1.28 (95% CI, 1.10 to 1.50), and 1.29 (95% CI, 1.11 to 1.51) per 1 SD increases in WC, WHtR, and BRI, respectively. The magnitudes of these associations were slightly enlarged after controlling for multiple variables (Model 2). To account for the baseline difference, relative changes in WC, WHtR, and BRI from baseline were also calculated (Supplementary Table 4), which showed similar results as above. Sensitivity analyses upon the exclusion of participants without fasting samples or using drugs for hypertension or dyslipidemia did not significantly affect the primarily outcomes (Supplementary Table 5).

Subgroup analyses showed that the association between changes in central fatness with risk of diabetes was not significantly affected by sex, age category, body weight status, history of smoking or drinking, or walking speed (all $p_{interaction} \geq 0.11$). However, the magnitude was larger in participants with overweight/obesity or in participants with slow walking speed compared with their counterparts (Supplementary Table 6).

Dose-response analyses noted that no evidence of a nonlinear relationship between changes in central fatness and risk of diabetes was observed in the whole population (all $p_{nonlinearity} \geq 0.11$) (Fig. 1), or specifically, in sex-stratified (all $p_{nonlinearity} \geq 0.06$) or overweight/obesity-based subgroups (all $p_{nonlinearity} \geq 0.24$).

Changes in central fatness had moderate predictive abilities for diabetes, with their AUROC ranging from 0.578 to 0.582 (Supplementary Fig. 3). There was no significant difference between the AUROC for changes in BMI and that for changes in WC, WHtR, or BRI (all $p \geq 0.64$ for compar-

Table 1. Baseline characteristics of participants

Characteristic	With incident diabetes	Without incident diabetes	*p* value
No. of participants	177	1,638	
Women, %	48.6	46.8	0.66
Smokers, %	45.8	43.9	0.63
Drinkers, %	33.3	33.3	0.99
Age, yr	67.1 ± 5.8	66.6 ± 5.6	0.14
Blood pressure			
SBP, mm Hg	134.4 ± 19.8	132.9 ± 21.9	0.19
DBP, mm Hg	75.5 ± 11.2	74.1 ± 11.4	0.06
Anthropometric measures			
Body weight, kg	58.1 ± 10.4	55.7 ± 9.8	< 0.01
BMI, kg/m^2	23.6 ± 3.4	22.5 ± 3.1	< 0.01
WC, m	0.88 ± 0.09	0.84 ± 0.09	< 0.01
WHtR	0.56 ± 0.06	0.54 ± 0.06	< 0.01
BRI	4.6 ± 1.3	4.1 ± 1.3	< 0.01
Biomarkers			
FPG, mg/dL[a]	104.8 ± 11.4	100.3 ± 10.7	< 0.01
HbA1c, %	5.3 ± 0.4	5.1 ± 0.4	< 0.01
TyG index[a]	8.7 ± 0.5	8.5 ± 0.5	< 0.01
TC, mg/dL	197.1 ± 36.8	192.9 ± 37.9	0.08
TG, mg/dL	138.0 ± 81.0	116.5 ± 65.3	< 0.01
HDL-C, mg/dL	49.4 ± 15.3	52.8 ± 15.1	< 0.01
LDL-C, mg/dL	119.9 ± 34.2	117.9 ± 34.5	0.23
UA, mg/dL	4.7 ± 1.3	4.5 ± 1.2	0.03
WBC, 10^9/L	6.7 ± 2.0	6.2 ± 1.9	< 0.01
lnCRP, mg/L	0.4 ± 1.1	0.2 ± 1.0	< 0.01
Cardiorespiratory fitness			
Walking speed, m/sec[b]	0.6 ± 0.2	0.6 ± 0.2	0.74

Values are presented as mean ± standard deviation.
SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; WHtR, waist-height ratio; BRI, body roundness index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TyG, triglycerides-and-glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; WBC, white blood cell; CRP, C-reactive protein.
[a]A total of 1,630 participants provided fasting blood samples.
[b]A total of 1,751 participants provided validated walking speed.

isons). Moreover, in the group of participants with stable BMI (defined as the middle tertile of the changes in BMI), similar results were observed but all the AUROC for changes in WC, WHtR, and BRI became non-significant from 0.50 (all $p \geq 0.08$).

Changes in central fatness and changes in cardiometabolic markers

Linear regression analyses adjusting for age, sex, and BMI showed that changes in WC, WHtR, or BRI were consistently and positively correlated with changes in HbA1c, TyG index, TG, WBC, and CRP in older adults (all $p \leq 0.04$) (Table 3).

Mediation analysis suggested that among the candidates

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Table 2. Changes in central fatness and risk of diabetes

Variable	No. of cases/total	OR (95% CI)		
		Unadjusted	Model 1[a]	Model 2[b]
Changes in WC				
Per 1 SD	177/1,815	1.31 (1.12–1.54)	1.34 (1.14–1.58)	1.42 (1.20–1.69)
Loss (Tertile 1, < –0.02 m)	36/610	0.50 (0.33–0.77)	0.50 (0.32–0.76)	0.42 (0.27–0.66)
Stable (Tertile 2, –0.02 to 0.03 m)	68/615	1 (reference)	1 (reference)	1 (reference)
Gain (Tertile 3, > 0.03 m)	73/590	1.14 (0.80–1.61)	1.20 (0.84–1.71)	1.21 (0.84–1.77)
Changes in WHtR				
Per 1 SD	177/1,815	1.28 (1.10–1.50)	1.32 (1.12–1.55)	1.41 (1.19–1.67)
Loss (Tertile 1, < –0.009)	36/605	0.51 (0.33–0.77)	0.50 (0.33–0.77)	0.42 (0.27–0.66)
Stable (Tertile 2, –0.009 to 0.019)	67/605	1 (reference)	1 (reference)	1 (reference)
Gain (Tertile 3, > 0.019)	74/605	1.12 (0.79–1.59)	1.19 (0.83–1.70)	1.24 (0.86–1.80)
Changes in BRI				
Per 1 SD	177/1,815	1.29 (1.11–1.51)	1.31 (1.12–1.53)	1.40 (1.19–1.66)
Loss (Tertile 1, < –0.18)	38/605	0.58 (0.38–0.88)	0.55 (0.36–0.84)	0.46 (0.30–0.73)
Stable (Tertile 2, –0.18 to 0.39)	63/605	1 (reference)	1 (reference)	1 (reference)
Gain (Tertile 3, > 0.39)	76/605	1.24 (0.87–1.76)	1.24 (0.87–1.79)	1.31 (0.90–1.90)

OR, odds ratio; CI, confidence interval; WC, waist circumference; SD, standard deviation; WHtR, waist-height ratio; BRI, body roundness index.
[a]Adjusted for age, sex, and body mass index.
[b]Adjusted for age, sex, body mass index, history of smoking and drinking, disease status (hypertension, dyslipidemia, and cardiovascular disease), systolic blood pressure, hemoglobin A1c, total cholesterol/high-density lipoprotein cholesterol, uric acid, C-reactive protein, and walking speed at baseline.

listed in Fig. 2, changes in HbA1c or TyG index met the mediation criteria for all the indicators of central fatness associated with risk of diabetes. Results showed further that the mediating effect was approximately 35% for changes in HbA1c and 21% for changes in TyG index for all the indicators of central fatness (Fig. 2).

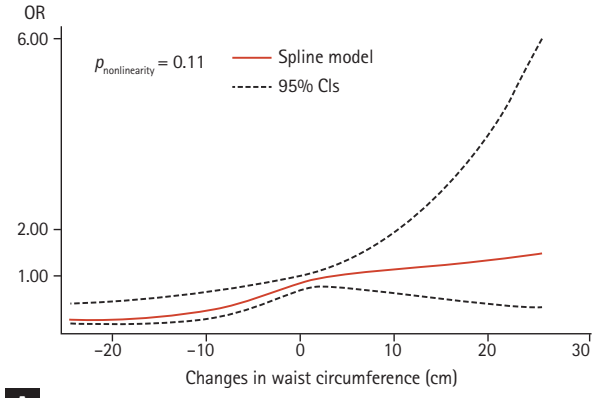
DISCUSSION

Main findings

This prospective cohort study showed several findings in older adults aged ≥ 60 years: (1) increases in central fatness (assessed by WC, WHtR, and BRI) were associated with elevated risk of diabetes in a dose-dependent manner; (2) changes in central fatness did not show superior predictive abilities for diabetes to changes in BMI—the indicator of general fatness; (3) increases in central fatness correlated with increases in HbA1c, TyG index, TG, WBC, and CRP, suggesting that gains in central fatness lead to deteriorated metabolic control; and (4) changes in HbA1c as well as in TyG index partly explained the association of risk of diabetes in relation to changes in central fatness.

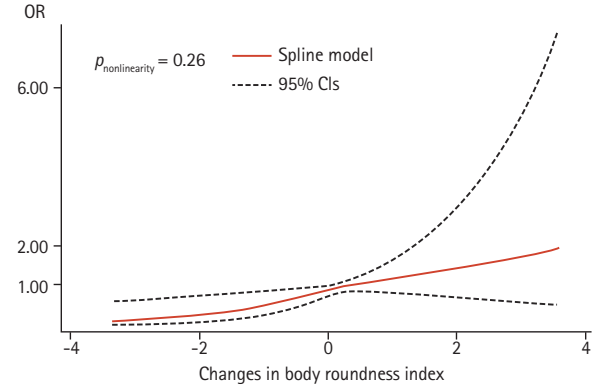
Interpretations and implications

A plenty of evidence has suggested that indicators of central fatness including WC and WHtR were positively associated with risk of diabetes [6,9]. However, no studies have evaluated the risk of diabetes in relation to changes in central fatness assessed by WC, WHtR, and BRI, in particular in older adults aged ≥ 60 years. As an attempt to address this issue, our study showed that increases in central fatness were re-



A Dose-response curve for changes in waist circumference

B Dose-response curve for changes in waist-height ratio



C Dose-response curve for changes in body roundness index

Figure 1. Dose-response analyses. (A) Dose-response analysis for changes in waist circumference, (B) dose-response analysis for changes in waist-height ratio, and (C) dose-response analysis for changes in body roundness index. All dose-response analyses were modeled with the restricted cubic splines with 3 knots at 10, 50, and 90 percentiles, and controlled for age, sex, body mass index, history of smoking and drinking (yes or no), systolic blood pressure, total cholesterol/high-density lipoprotein cholesterol, uric acid, C-reactive protein, and walking speed at baseline. OR, odds ratio; CI, confidence interval.

lated to elevated risk of diabetes, and that the association was dose-dependently and linearly shaped (as evidenced by our dose-response analysis). Moreover, our subgroup analysis found that in participants with fast walking speed at baseline, increases in central fatness did not result in significantly increased risk of diabetes, with its magnitude being much smaller than that in participants with slow walking speed. This may probably suggest that good physical performance could help to minimize the adverse effect from gains in central fatness, at least partly.

In recent years there has been an ongoing interest in exploring which or the change of which anthropometric index related to obesity shows the largest predictive ability for diabetes [6,9,10,23-25]. Despite no consensus has been reached to date, accumulating evidence has shown that the indicators of central fatness (such as WC) or their changes outperformed the indicator of general fatness (that is, BMI) in predicting diabetes [6,10]. However, in our study we observed similar AUROC for these indicators regarding their changes, even among participants with stable BMI, suggesting that there might be no significant difference on their predictive abilities. It is speculated that this discrepancy between previous studies and ours might be due to the differences in target populations (older versus middle-aged adults).

Notably, our present study showed for the first time that increases in central fatness were related to deteriorated glycemic control (represented by HbA1c), worsened lipid profile (assessed by TG), and greater degree of inflammation (reflected by WBC and CRP). These results may provide some evidence in support of the findings that weight reductions promote cardiometabolic health, such as improving glycemic control as well as lowering inflammation [11]; while importantly, they shed some insights into the mechanism(s) underlined for diabetes in relation to changes in central fatness. Yet we found that only changes in HbA1c and TyG index were identified as potential mediators. Since

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Table 3. Multi-variable linear regression analyses for changes in central fatness with changes in cardiometabolic markers

Variable	Changes in WC		Changes in WHtR		Changes in BRI	
	Sβ[a]	*p* value	Sβ[a]	*p* value	Sβ[a]	*p* value
Blood pressure						
Change in SBP	0.05	0.03	0.04	0.12	0.04	0.10
Change in DBP	0.03	0.22	0.02	0.49	0.02	0.46
Glycemic control						
Change in FPG[b]	0.05	0.06	0.05	0.07	0.04	0.09
Change in HbA1c	0.07	< 0.01	0.06	0.01	0.07	< 0.01
Change in TyG index[b]	0.09	< 0.01	0.08	< 0.01	0.08	< 0.01
Lipid profiles						
Change in TC	0.04	0.14	0.04	0.06	0.05	0.05
Change in TG	0.10	< 0.01	0.10	< 0.01	0.10	< 0.01
Change in HDL-C	−0.06	0.02	−0.04	0.06	−0.04	0.07
Change in LDL-C	0.02	0.37	0.03	0.20	0.03	0.20
Inflammatory markers						
Change in WBC	0.05	0.04	0.05	0.02	0.05	0.02
Change in CRP[c]	0.09	< 0.01	0.09	< 0.01	0.09	< 0.01

CI, confidence interval; WC, waist circumference; WHtR, waist-height ratio; BRI, body roundness index; Sβ, standardized correlation coefficient; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TyG, triglycerides and glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; CRP, C-reactive protein.
[a]Adjusted for age, sex, and body mass index.
[b]A total of 1,630 participants provided fasting blood samples.
[c]CRP was ln-transformed prior to the regression analysis.

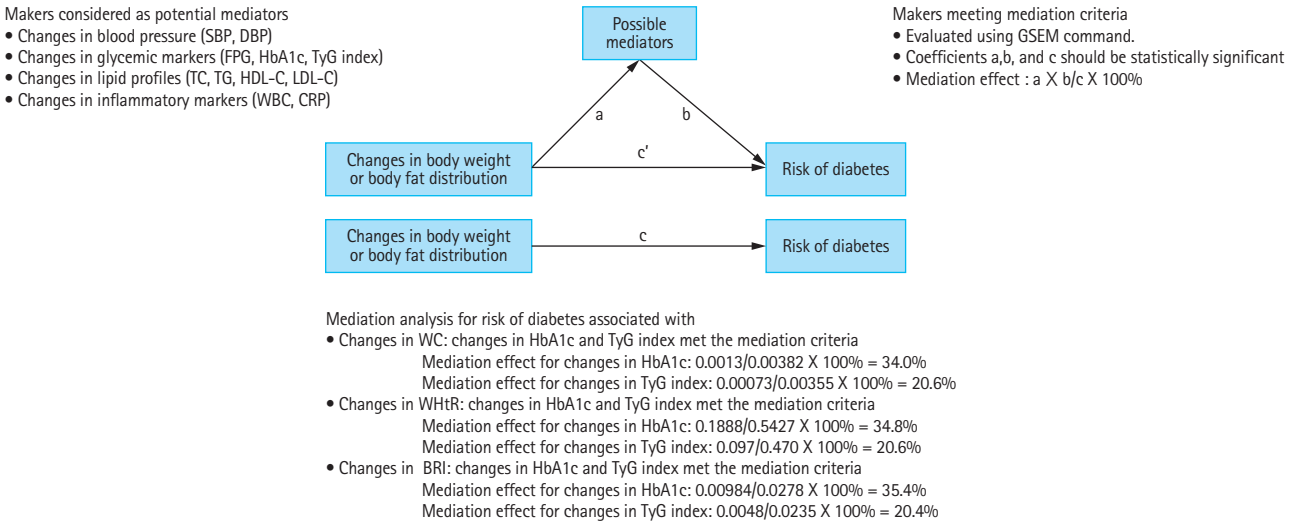

Figure 2. Mediation analysis for risk of diabetes associated with changes in central fatness and risk of diabetes. SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TyG, triglycerides-and-glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell; CRP, C-reactive protein; GSEM, generalized structural equation model; WC, waist circumference; WHtR, waist-height ratio; BRI, body roundness index.

HbA1c is a biomarker linking with chronic hyperglycemia and TyG index is a reliable indicator for insulin resistance [15], it is likely that deteriorations in glycemic control and insulin resistance may mediate the impact of increases in central fatness on risk of diabetes. However, it should be mentioned that their total mediating effects account for only about 56%. In this regard, future studies that explore the mediation effect from other possible contributors such as cell adhesion molecules [26], adipokines [27], and myokines [28], are worth being conducted.

Strengths and limitations

The strengths of our study include a prospective cohort design, a lab-based clarification of diabetes, the direct measurement of anthropometric parameters that avoid recall bias, and the use of multiple indicators of central fatness. However, this study has several limitations. First, the relatively short follow-up period could not reflect the influences of long-term changes in central fatness on risk of diabetes in older adults. Second, there still exists the possibility of residual confounding from the unmeasured factors such as cytokine changes, although we controlled for multiple variables in our analyses. Third, there is evidence that the use of statin or antihypertensive medication (e.g., diuretics or beta-blockers) might be associated with increased risk of diabetes [29,30]. Yet we were not able to assess the influence of these medications on the association between changes in central fatness and risk of diabetes due to the issue that such information was not collected in CHARLS. Fourth, we could not determine whether the changes in central fatness were gradual or uneven, while this may affect their relationship with risk of diabetes. Finally, our protocol for measuring walking speed, although has been also adopted in the Health and Retirement Study [31], is different from the recommended one—6-m walking test by the Asian Working Group for Sarcopenia [32]. This may potentially affect the assessment of one's physical performance.

In conclusion, increases in central fatness were related to elevated risk of diabetes in a dose-dependent manner, but this association was not persisted in participants with good physical performance. The association of increases in central fatness with elevated risk of diabetes was underlined by deteriorated glycemic control and insulin resistance, at least partly.

KEY MESSAGE

1. Increases in waist circumference, waist-height ratio, and body roundness index were related to elevated risk of diabetes in elderly.
2. The observed association was not persisted in participants with good physical fitness.
3. Increases in central fatness were associated with poor control in metabolic profiles.
4. Changes in hemoglobin A1c and triglycerides-and-glucose index may partly explain the observed association.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Characteristics of the comorbidities and medication use at baseline

Variable	With incident diabetes	Without incident diabetes	*p* value
No. of participants	177	1,638	
Comorbidities			
Hypertension	95	740	0.03
Dyslipidemia	82	648	0.08
Chronic lung disease	26	212	0.51
Cardiovascular disease	28	209	0.23
Kidney disease	12	99	0.69
Arthritis	69	634	0.91
Medication use for the following comorbidities[a]			
Hypertension[b]	50	329	0.01
Dyslipidemia[b]	11	74	0.31
Chronic lung disease[b]	15	150	0.76
Cardiovascular disease[b]	19	142	0.36
Kidney disease[b]	5	55	0.71
Arthritis[b]	35	297	0.59

[a]The information was collected by using the questionnaire of "Do you take Chinese traditional medicine or Western modern medicine to treat or control the disease of …?."
[b]Categories of the drugs used were not specified in the China Health and Retirement Longitudinal Study.

Supplementary Table 2. Central fatness at baseline and risk of diabetes

Variable	OR (95% CI)		
	Unadjusted	Model 1[a]	Model 2[b]
Per 1 SD higher of WC at baseline	1.48 (1.27–1.73)	1.43 (1.09–1.89)	1.44 (1.07–1.92)
Per 1 SD higher of WHtR at baseline	1.45 (1.25–1.69)	1.46 (1.09–1.95)	1.40 (1.02–1.90)
Per 1 SD higher of BRI at baseline	1.43 (1.24–1.66)	1.43 (1.07–1.89)	1.37 (1.02–1.85)

OR, odds ratio; CI, confidence interval; SD, standard deviation; WC, waist circumference; WHtR, waist-height ratio; BRI, body roundness index.
[a]Adjusted for age, sex, and body mass index.
[b]Adjusted for age, sex, body mass index, history of smoking and drinking, disease status (hypertension, dyslipidemia and cardiovascular disease), systolic blood pressure, hemoglobin A1c, total cholesterol/high-density lipoprotein cholesterol, uric acid, and walking speed at baseline.

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Supplementary Table 3. Baseline characteristics of participants among tertiles of changes in central fatness

Characteristic	Loss (Tertile 1)	Stable (Tertile 2)	Gain (Tertile 3)	*p* value[a]
From changes in WC				
Age, yr	67.1 ± 6.0	66.4 ± 5.4	66.4 ± 5.6	0.02
BMI, kg/m^2	22.7 ± 3.3	22.8 ± 3.2	22.4 ± 3.0	0.13
Blood pressure				
SBP, mmHg	134.2 ± 22.1	132.6 ± 21.5	132.1 ± 21.5	0.22
DBP, mmHg	74.4 ± 11.4	73.9 ± 11.4	74.3 ± 11.4	0.68
Biomarkers				
FPG, mg/dL[b]	101.0 ± 11.8	100.9 ± 10.2	100.4 ± 10.4	0.59
HbA1c, %	5.1 ± 0.40	5.1 ± 0.4	5.1 ± 0.4	0.93
TC, mg/dL	194.2 ± 40.0	193.9 ± 37.6	191.8 ± 35.7	0.50
TG, mg/dL	116.9 ± 68.2	121.1 ± 73.1	117.6 ± 68.2	0.52
HDL-C, mg/dL	53.6 ± 16.3	51.6 ± 14.4	52.2 ± 14.6	0.07
LDL-C, mg/dL	117.9 ± 36.9	118.6 ± 34.2	117.7 ± 32.0	0.87
UA, mg/dL	4.6 ± 1.3	4.6 ± 1.2	4.4 ± 1.2	0.01
WBC, 10^9/L	6.3 ± 2.0	6.2 ± 1.8	6.2 ± 1.9	0.68
lnCRP, mg/L	0.3 ± 1.1	0.2 ± 1.0	0.1 ± 1.0	0.06
From changes in WHtR				
Age, yr	66.9 ± 5.8	66.4 ± 5.4	66.5 ± 5.7	0.23
BMI, kg/m^2	22.7 ± 3.3	22.8 ± 3.2	22.4 ± 2.9	0.05
Blood pressure				
SBP, mmHg	133.0 ± 21.3	133.6 ± 22.3	132.4 ± 21.4	0.65
DBP, mmHg	74.2 ± 11.2	74.2 ± 11.6	74.3 ± 11.2	0.99
Biomarkers				
FPG, mg/dL[b]	101.1 ± 11.8	100.5 ± 10.2	100.7 ± 10.3	0.62
HbA1c, %	5.1 ± 0.4	5.1 ± 0.4	5.1 ± 0.4	0.30
TC, mg/dL	194.3 ± 40.1	195.3 ± 37.9	190.5 ± 35.2	0.07
TG, mg/dL	117.8 ± 69.3	120.0 ± 72.9	118.1 ± 67.5	0.84
HDL-C, mg/dL	53.4 ± 16.1	52.2 ± 14.8	51.8 ± 14.5	0.17
LDL-C, mg/dL	117.8 ± 36.4	120.0 ± 35.5	116.4 ± 31.1	0.18
UA, mg/dL	4.6 ± 1.3	4.6 ± 1.2	4.4 ± 1.2	0.01
WBC, 10^9/L	6.3 ± 2.0	6.2 ± 1.8	6.2 ± 1.9	0.63
lnCRP, mg/L	0.2 ± 1.1	0.2 ± 1.0	0.1 ± 1.0	0.11
From changes in BRI				
Age, yr	67.0 ± 5.8	66.4 ± 5.4	66.5 ± 5.7	0.18
BMI, kg/m^2	22.7 ± 3.3	22.5 ± 3.2	22.6 ± 3.0	0.49
Blood pressure				
SBP, mmHg	133.1 ± 21.2	133.2 ± 22.4	132.8 ± 21.4	0.94
DBP, mmHg	74.3 ± 11.2	74.0 ± 11.6	74.4 ± 11.3	0.88
Biomarkers				
FPG, mg/dL[b]	101.3 ± 11.8	100.4 ± 10.3	100.6 ± 10.3	0.39
HbA1c, %	5.1 ± 0.4	5.1 ± 0.4	5.1 ± 0.4	0.31
TC, mg/dL	194.4 ± 40.0	193.8 ± 38.1	191.7 ± 35.1	0.43

Supplementary Table 3. Continued

Characteristic	Loss (Tertile 1)	Stable (Tertile 2)	Gain (Tertile 3)	*p* value[a]
TG, mg/dL	118.5 ± 69.4	117.8 ± 72.5	119.6 ± 67.9	0.90
HDL-C, mg/dL	53.2 ± 16.1	52.5 ± 14.7	51.7 ± 14.6	0.19
LDL-C, mg/dL	117.9 ± 36.5	118.8 ± 35.5	117.5 ± 31.2	0.80
UA, mg/dL	4.6 ± 1.3	4.6 ± 1.2	4.4 ± 1.2	0.01
WBC, 10^9/L	6.3 ± 2.1	6.2 ± 1.8	6.2 ± 1.9	0.45
lnCRP, mg/L	0.2 ± 1.1	0.2 ± 1.0	0.1 ± 1.0	0.17

Values are presented as mean ± standard deviation.
WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; WBC, white blood cell; CRP, C-reactive protein; WHtR, waist-height ratio; BRI, body roundness index
[a]It was compared using one-way analysis of variance.
[b]A total of 1,630 participants provided fasting blood samples.

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Supplementary Table 4. Relative changes in central fatness from baseline and risk of diabetes[a]

Variable	No. of cases/total	OR (95% CI)		
		Unadjusted	Model 1[b]	Model 2[c]
Per 1 SD higher of relative change in WC	177/1,815	1.27 (1.08–1.48)	1.31 (1.11–1.53)	1.38 (1.16–1.64)
Per 1 SD higher of relative change in WHtR	177/1,815	1.25 (1.07–1.45)	1.29 (1.10–1.52)	1.38 (1.16–1.64)
Per 1 SD higher of relative change in BRI	177/1,815	1.19 (1.03–1.38)	1.24 (1.06–1.44)	1.32 (1.12–1.55)

OR, odds ratio; CI, confidence interval; SD, standard deviation; WC, waist circumference; WHtR, waist-height ratio; BRI, body roundness index.

[a]Relative changes were calculated as the change scores divided by the baseline score.

[b]Adjusted for age, sex, and body mass index.

[c]Adjusted for age, sex, body mass index, history of smoking and drinking, disease status (hypertension, dyslipidemia and cardiovascular disease), systolic blood pressure, hemoglobin A1c, total cholesterol/high-density lipoprotein cholesterol, uric acid, C-reactive protein, and walking speed at baseline.

Supplementary Table 5. Sensitivity analyses[a]

Sensitivity analyses	OR (95% CI)
Excluding participants without fasting samples (n = 398)	
Per 1 SD higher of relative change in WC	1.41 (1.16–1.72)
Per 1 SD higher of relative change in WHtR	1.38 (1.13–1.67)
Per 1 SD higher of relative change in BRI	1.36 (1.13–1.64)
Excluding participants using drugs for hypertension (n = 379)	
Per 1 SD higher of relative change in WC	1.36 (1.12–1.66)
Per 1 SD higher of relative change in WHtR	1.35 (1.11–1.65)
Per 1 SD higher of relative change in BRI	1.36 (1.12–1.66)
Excluding participants using drugs for dyslipidemia (n = 85)	
Per 1 SD higher of relative change in WC	1.42 (1.19–1.69)
Per 1 SD higher of relative change in WHtR	1.40 (1.18–1.70)
Per 1 SD higher of relative change in BRI	1.40 (1.18–1.65)

OR, odds ratio; CI, confidence interval; SD, standard deviation; WC, waist circumference; WHtR, waist-height ratio; BRI, body roundness index.

[a]Adjusted for age, sex, body mass index, history of smoking and drinking, systolic blood pressure, hemoglobin A1c, total cholesterol/high-density lipoprotein cholesterol, uric acid, C-reactive protein, and walking speed at baseline.

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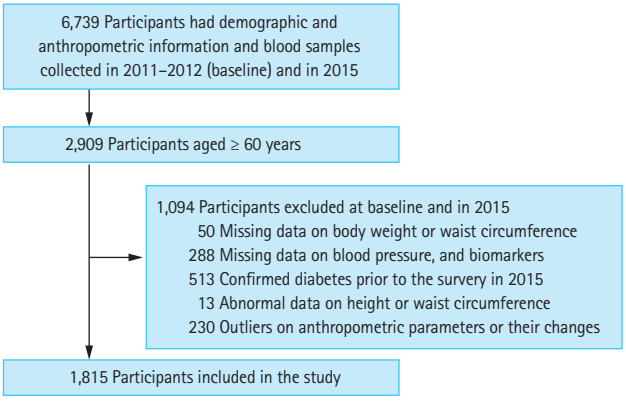
Supplementary Table 6. Subgroup analyses[a]

Subgroup	Per 1 SD change in waist circumference		Per 1 SD change in waist-height ratio		Per 1 SD change in body roundness index	
	OR (95% CI)	*p* value[b]	OR (95% CI)	*p* value[b]	OR (95% CI)	*p* value[b]
Sex		0.27		0.17		0.11
Male	1.49 (1.17–1.88)		1.51 (1.18–1.94)		1.56 (1.21–2.02)	
Female	1.24 (0.99–1.55)		1.20 (0.97–1.49)		1.20 (0.98–1.46)	
Age status, yr		0.87		0.87		0.77
60–70	1.35 (1.12–1.64)		1.30 (1.08–1.58)		1.29 (1.08–1.55)	
≥ 70	1.31 (0.97–1.77)		1.34 (0.99–1.82)		1.36 (1.01–1.83)	
Overweight/obesity		0.21		0.44		0.58
With	1.56 (1.18–2.07)		1.45 (1.11–1.90)		1.40 (1.10–1.78)	
Without	1.25 (1.02–1.54)		1.27 (1.03–1.55)		1.28 (1.04–1.58)	
Smoking		0.48		0.69		0.54
Yes	1.42 (1.04–1.93)		1.38 (1.06–1.81)		1.41 (1.08–1.85)	
No	1.23 (0.95–1.58)		1.29 (1.05–1.58)		1.27 (1.05–1.55)	
Drinking		0.65		0.59		0.41
Yes	1.42 (1.07–1.90)		1.41 (1.05–1.89)		1.46 (1.08–1.96)	
No	1.31 (1.07–1.59)		1.28 (1.06–1.56)		1.26 (1.05–1.52)	
Walking speed[c]		0.26		0.13		0.13
Fast	1.24 (0.98–1.58)		1.18 (0.93–1.50)		1.18 (0.93–1.49)	
Slow	1.50 (1.19–1.88)		1.52 (1.21–1.91)		1.51 (1.21–1.88)	

SD, standard deviation; OR, odds ratio; CI, confidence interval.
[a]Adjusted for age, sex, and body mass index.
[b]It indicates the interaction effect.
[c]The upper half was defined as fast group and the lower one was as slow group.



Supplementary Figure 1. Flowchart.

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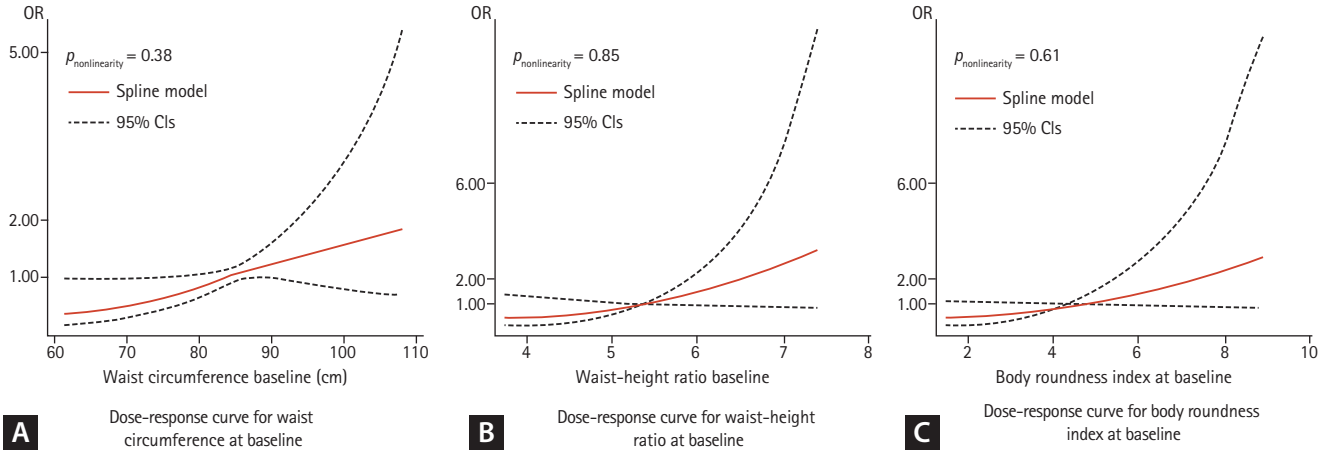
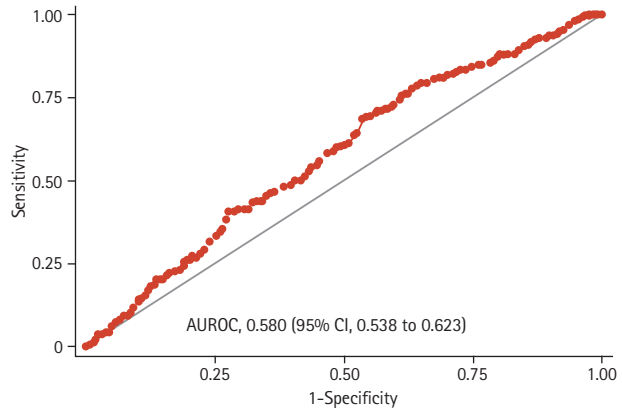
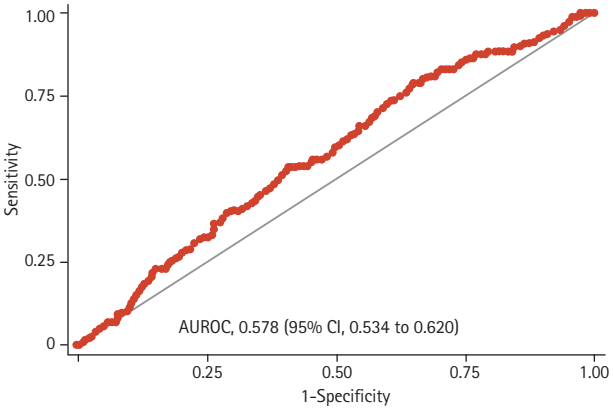


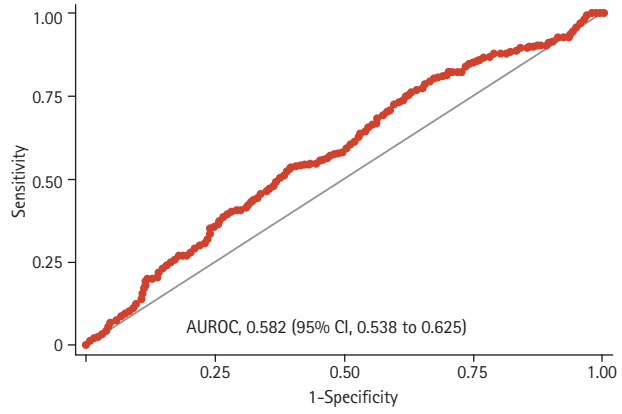
Supplementary Figure 2. Dose-response analyses for central fatness at baseline. (A) Dose-response analysis for waist circumference at baseline, (B) dose-response analysis for waist-height ratio at baseline, and (C) dose-response analysis for body roundness index at baseline. All dose-response analyses were modeled with the restricted cubic splines with 3 knots at 10, 50, and 90 percentiles, and controlled for age, sex, body mass index, history of smoking and drinking (yes or no), systolic blood pressure, total cholesterol/high-density lipoprotein cholesterol, uric acid, and walking speed at baseline. OR, odds ratio; CI, confidence interval.



A Changes in waist circumference



B Changes in waist-height ratio



C Changes in body roundness index

Supplementary Figure 3. Area under the receiver operating characteristic curve (AUROC) for changes in central fatness. (A) Changes in waist circumference, (B) change in waist-height ratio, and (C) changes in body roundness index. CI, confidence interval.

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